J. Org. Chem. 1987, *52*, 4369–4377

New Approaches to the Synthesis of Vitamin D Metabolites. 2.[1] The Effect of Some Substituents on Stereochemistry in the Intramolecular Cycloadditions of Nonatrienes

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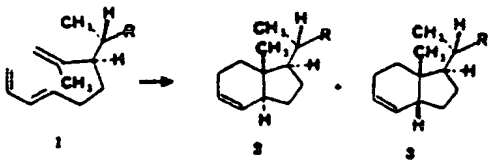
Received December 23, 1986

Intramolecular Diels–Alder reactions of 8-methyl-1,3,8-nonatrienes **5** and **6** were studied to determine the effects of substituents on the stereochemistry of ring closure. Substituents at C-3 favor closure to *trans*-hydrindenes; likewise, a C-7 alkyl group favors closure to *trans*-hydrindene products. Substrates bearing a C-7 alkyl substituent afforded products in which the alkyl substituent was invariably cis to the angular methyl group (**34** and **35**). The ratio of trans:cis fused hydrindenes was shown to be solvent-dependent; yields were improved when closures were effected in dimethylaniline.

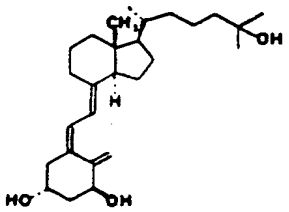
In our previous paper,[1] we reported that the Diels–Alder closure of trienes **1**,[2] prepared by a sequence based on the Ireland–Claisen rearrangement, gave only two of the four possible hydrindenes, the desired *trans,anti*-**2** and the *cis,anti*-**3**. In order to develop further this approach to vitamin D derivatives[3] (for example, 1,25-dihydroxyvitamin D_3, **4**), we considered ways to modify the cyclization substrate so that closure to a *trans,anti*-hydrindene structure would be favored over closure to a cis,anti epimer.



1 **2** **3**

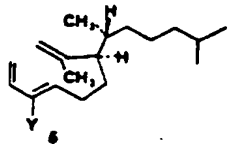
a R = CH_2OH

b R = CO_2CH_3



4 (lit. 25-$(OH)_2D_3$)

The structural requirements of the eventual target compounds define the number and positions of substituents for hydrindenes which might serve as attractive synthetic intermediates; the corresponding limitations on triene precursors led us to consider substrates of general structure **5**. In view of the restrictions on the triene substrates, it was encouraging to inspect the conformations required for closure of **5**, in particular **5a–c**.



5 **6**

a Y = CH_3

b Y = Br

c Y = $CH_2SC_6H_5$

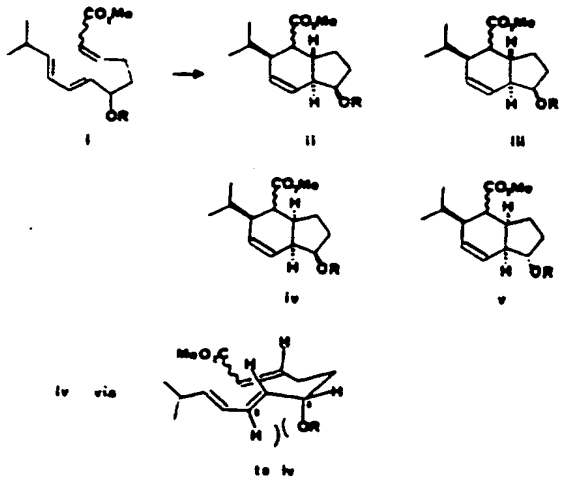
Conformations A and B that would lead to the syn products are considered unlikely because of interactions involving the C-7 (latent steroidal C-17) side chain.[1,3b] W postulated that conformation C would be disfavored relative to conformation D as a result of the interaction between the C-3 substituent and the C-5 "axial" H;[4] thus,

(1) Part 1: Parker K. A., Iqbal, T. I. *J. Org. Chem.* 1982, *47*, 337.

(2) For reviews on the intramolecular Diels–Alder reaction see: (a) Fallis, A. G. *Can. J. Chem.* 1984, *62*, 183–234. (b) Taber, D. F. *Intramolecular Diels Alder and Alder Ene Reactions, Reactivity and Structure Concepts in Organic Chemistry*, Vol. 18, 1984. Springer-Verlag: New York; (c) Ciganek, E. *Org. React. (N.Y.)* 1984, *32*, 1–374.

(3) Our strategy for the synthesis of appropriate hydrindene intermediates (consider structures **34b** or **34c**) is based on an Ireland ester–enolate Claisen rearrangement (to establish a potentially dienophilic olefin adjacent to two chiral centers), followed by an intramolecular Diels–Alder closure (which would establish the two additional chiral centers required). The independent work of Wilson is also based on a coupling of the Claisen rearrangement with the intramolecular Diels–Alder reaction: (a) Wilson, S. R.; Haque, M. S. *Tetrahedron Lett.* 1984, *25*, 3147; see also the following paper which completes the synthesis of vitamin D_3. (b) Wilson, S. R.; Haque, M. S. *J. Org. Chem.* 1982, *47*, 5413.

(4) The relevant experiments at the time were those of Roush. Roush had shown that the *E* and *Z* esters **i** underwent closure to give a mixture which contained **ii**, **iii**, and **v**, but in each case, very little **iv**. This result demonstrates that for trienes **i**, the transition state ts **iv** (shown) is of higher energy than the transition states leading to **ii**, **iii**, and **v**; Roush suggested that the relatively high energy of ts **iv** is the result of the C(8)-H/C(6)-axial OR interaction indicated. We reasoned that the inverse situation, in which there exists a C(3)-Alkyl/C(5)-axial H (compare ts **iv** with conformation C in the text), would result in an analogous increase in the energy of this transition state which lies on the path to the undesired *cis*-hydrindene **3**.



i **ii** **iii** **iv** **v**

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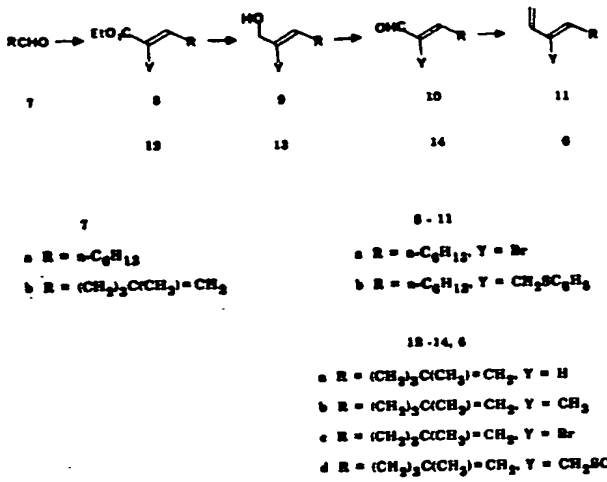
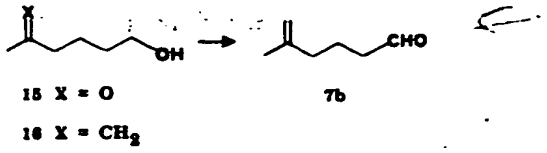
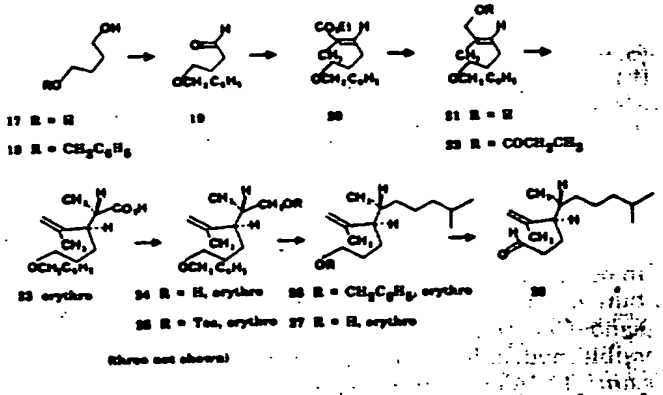
Scheme I



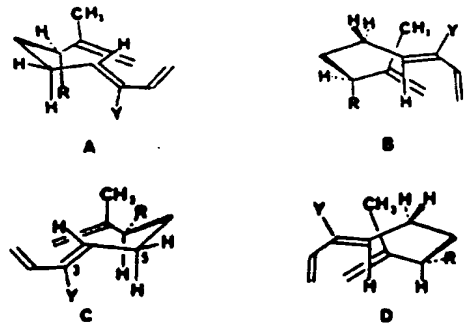
Scheme II



Scheme III



conformation D, which would lead to the desired trans,anti product, appeared to be the best of the four possible transition-state conformations.



In order to test the premise that a C-3 substituent would favor the *trans*-hydrindene product,[5,6] and also to prepare compounds that might serve as useful intermediates, we have prepared a number of 3-substituted 1,3,8-nonatrienes (6) and 3,7-disubstituted nonatrienes (5) and examined the stereochemistry of their thermal cycloadditions.

Choice of C-3 Substituents. For these limited systematic studies, we chose trienes 5 and 6 in which the C-3 substituent varied and included hydrogen, methyl, bromo, and (phenylthio)methyl groups. We imagined that each general structure could be derived from a common precursor aldehyde by a four-step sequence (Emmons–Wadsworth condensation, reduction, oxidation, Wittig condensation—see Scheme I). The preparation of unsubstituted (*E*)-dienes by this route appeared to be straighforward. However, we had had no experience with the chemistry of the bromo and (phenylthio)methyl substituted systems. Therefore, before proceeding to the preparation of cyclization substrates, we attempted the syntheses of model dienes 11a and 11b.

The preparation of bromo diene 11a was based on the condensation of (α-bromocarbethoxy)methylenetriphenylphosphorane[7] with heptanal; geometrically clean *Z* ester 8a was easily obtained by chromatographic separation from the minor *E* isomer. Reduction of 8a with DIBAL gave alcohol 9a; oxidation with PCC gave aldehyde 10a; Wittig condensation in 84% yield completed the synthesis of diene 11a.

(*E*)-1-(Phenylthio)-2-(ethoxycarbonyl)-2-nonene (8b) was prepared according to Semmelhack from heptaldehyde and the β-(phenylthio)methyl-substituted Emmons reagent.[8] Reduction of ester 8b with diisobutylaluminum hydride (DIBAL) gave the alcohol 9b (94% yield), which was oxidized in good yield (73%) to the aldehyde 10b by pyridinium dichromate (PDC).[9] Wittig condensation gave the desired diene 11b in 88% yield.

Preparation of Cyclization Substrates. Having established viable routes to the diene moieties, we turned to synthesis of cyclization substrates 5 and 6. The key intermediate for the preparation of the trienes 6 was aldehyde 7b.[10] This was conveniently obtained from 6-hydroxy-2-hexanone (15)[11] by Wittig reaction to give the olefin 16[12] and pyridinium chlorochromate (PCC) oxidation (Scheme II).

Aldehyde 7b could be converted to each of the α,β-unsaturated esters 12 by condensation with the appropriately substituted Emmons–Wadsworth reagent. The two-step reduction–oxidation procedure converted each ester 12 to the corresponding aldehyde 14; Wittig condensation converted each aldehyde 14 to the desired triene 6.

The key intermediate for the synthesis of trienes 5 was aldehyde 28. The preparation of 28 (Scheme III) began with the benzylation of 1,4-butanediol (17) with benzyl

(5) Recent work in several groups (including that of Wilson, ref 3) has shown that a C-3 substituent does indeed favor the formation of *trans*-hydrindenes in related Diels–Alder closures: (a) Ichihara, A.; Kimura, R.; Yamada, S.; Sakamura, S. *J. Am. Chem. Soc.* **1980**, *102*, 6353. (b) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121. (c) Kametani, T.; Matsumoto, H.; Honda, T.; Fukumoto, K. *Tetrahedron Lett.* **1980**, *21*, 4847. Kametani, T.; Matsumoto, H.; Honda, T.; Nagai, M.; Fukumoto, K. *Tetrahedron* **1981**, *37*, 2555. (d) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421.

(6) Related steric effects have been observed in the closure of 1,3,9-decatrienes; see ref 5d and (a) Wilson, S. R.; Haque, M. S.; Misra, R. N. *J. Org. Chem.* **1982**, *47*, 747. Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289. (b) Marshall, J. A.; Audia, J. E.; Grote, *J. J. Org. Chem.* **1986**, *51*, 1157. Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893.

(7) (a) This reagent was first prepared by Denny, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998. These workers did not report its use however. (b) Boeckman and Ko reported the use of this reagent for the preparation of *Z* α-bromo α,β-unsaturated esters and the use of DIBAL for the subsequent reduction of these products: Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.

(8) Semmelhack, M. F.; Tomesch, J. C.; Czarny, M.; Boettger, S. *J. Org. Chem.* **1978**, *43*, 1259.

(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(10) Wilson, R. M.; Rekers, J. W.; Packard, A. B.; Elder, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 1633.

(11) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799.

(12) Eschenmoser, A.; Frey, A. *Helv. Chim. Acta* **1952**, *35*, 1660.

Scheme IV

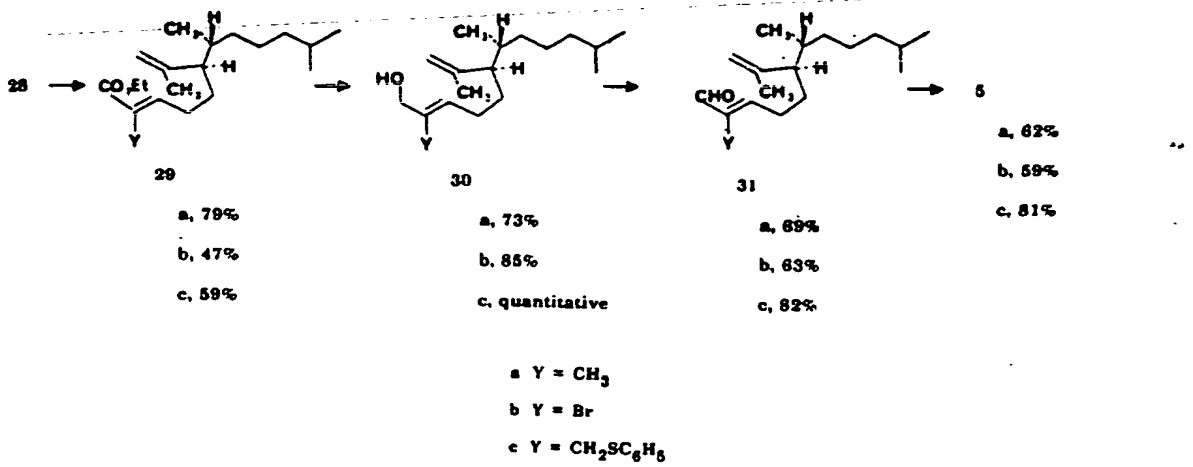


Table I. Product Ratios and Yields

substrate	products	ratio trans:cis (yield, %)[a] (solvent: C_6H_6 or $C_6H_5CH_3$)	conditions[b]	ratio trans:cis (yield, %) (solvent: DMA)	conditions[b]
6a, Y = H	32a + 33a	0.33[c]	200 °C, 10 h, DTBH	0.70 (61)	reflux, 48 h, DTBH
6b, Y = CH_3	32b + 33b	0.67 (50)	220 °C, 18 h, MB	3.6 (80)	reflux, 12 h, DTBH
6c, Y = Br	32c + 33c	0.70[c]	200 °C, 6 h, MB	1.0 (70)	reflux, 20 h, DTBH
6d, Y = $CH_2SC_6H_5$	32d + 33d	0.50 (55)	200 °C, 70 h, MB	1.7 (78)	reflux, 4 h, DTBH
1a	2a + 3a	1.0 (23)[d]	200 °C, 18 h		
1b	2b + 3b	1.0 (quant)[d]	200 °C, 6 h		
5a, Y = CH_3	34a + 35a	3.0 (62)	200 °C, 18 h, DTBH	3.0 (93)	reflux, 30 h, DTBH
5b, Y = Br	34b + 35b	1.3 (71)	200 °C, 60 h, MB	1.8 (86)	reflux, 12 h, DTBH
5c, Y = $CH_2SC_6H_5$	34c + 35c	1.0 (50)	210 °C, 18 h, DTBH	2.5 (80)	reflux, 2 h, DTBH

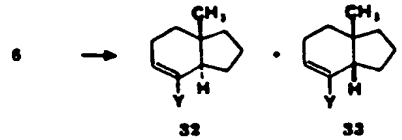
[a] Substrates 6a–c and 1a and 1b were cyclized in benzene; 6d and 5a–c were cyclized in toluene (see Experimental Section). [b] Radical inhibitor: di-*tert*-butylhydroquinone (DTBH) or methylene blue (MB). [c] Yield less than 20%. [d] Data from ref 1.

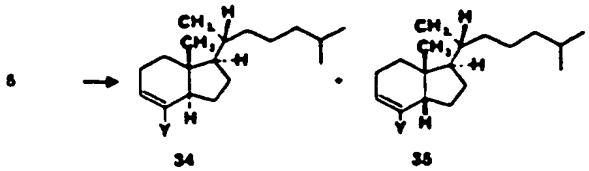
br mide and sodium hydride in DMF. After removal of minor amounts of the dibenzyl ether by flash chromatography, alcohol 18 was obtained in 48% yield. Oxidation with PCC to aldehyde 19 proceeded in 78% yield. Chain extension with triethyl 2-phosphonopropionate gave the unsaturated ester 20 in 89% yield. Reduction to the allylic alcohol ($LiAlH_4$, 80% yield) and esterification (propionyl chloride, pyridine, 83%) gave the ester 22.

Ireland–Claisen rearrangement[13] of propionate 22, which fixed the relative stereochemistry at the latent steroidal C-17 and C-20, was effected by treatment with 2.2 equiv f lithium diisopropylamide (LDA) in THF at 78 °C. A 76% yield of a 5:1 erythro:threo mixture of carboxylic acids 23 (see Experimental Section) was obtained from this procedure. This mixture was reduced with lithium aluminum hydride to the corresponding mixture of diastereomeric alcohols 24 (erythro, C-2 methyl at 0.89 ppm, J = 6.9 Hz; threo C-2 methyl at 0.97 ppm, J = 6.6 Hz) in 87% yield. Copper-catalyzed Grignard coupling[14] via the tosylates 25 (73% yield) gave a mixture of benzyl ethers 26 (85% yield); deprotection with sodium/ammonia gave the alcohols 27 (quantitative yield), which were separated by medium pressure chromatography. The major diastereomer, erythro alcohol 27 (C-methyl doublet at 0.80 ppm, J = 6.9 Hz) was oxidized by Collins' reagent to the key aldehyde 28 (91% yield).

Aldehyde 28 was converted by the four-step diene syntheses to trienes 5a–c. Yields for the steps of these sequences are noted in Scheme IV; details of these transformations are recorded in the Experimental Section.

Cyclization of Substituted Nonatrienes. The thermal cyclizations of the two series of trienes, 6 and 5, were effected by heating in benzene or toluene (sealed tube). A second set of experiments in which *N,N*-dimethylaniline (DMA) was employed as the solvent (reflux under nitrogen) was also carried out. Yields and product ratios for both sets of experiments are shown in Table I. In all cases but one, product ratios were assigned by analysis of the ^1H NMR spectrum of the hydrindene mixture.





For the simple hydrindenes 32a and 33a, assignment of ring juncture stereochemistry was straightf rward: the higher field methyl singlet was assigned to the *trans*-hydrindene[15] in each mixture. Correlation of the inte-

(13) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(14) Lythgoe, B.; Roberts, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2608.

gration values for the methyl singlets with the integration values for the vinyl proton peaks in hydrindene mixtures **32b/33b**, **32c/33c**, and **32d/33d** revealed that, in each pair, the vinyl proton of the *trans*-hydrindene appeared at higher field than the vinyl proton of the *cis*-hydrindene. Although this correlation is based on a limited number of examples, we feel that it is general, at least in the absence of shift-inducing substituents.

The ratio of **32a:33a** was calculated from the ratio of the integrals of the sharp high field methyl singlets.

The ratios of **32b:33b**, **32c:33c**, and **32d:33d** were most accurately calculated from the ratios of the integrals of the vinyl proton signals.

Hydrindenes **34a** and **35a** were separated by silver nitrate chromatography. The faster moving product, isolated in 69% yield, exhibited a three-proton singlet at 0.67 ppm and a one-proton broad singlet at 5.21 ppm. The slower moving product, isolated in 23% yield, had a three-proton singlet at 0.89 ppm and a one-proton broad singlet at 5.36 ppm. We assigned the ratio of **34a:35a** as 3:1 on the basis of the yields of these isolated compounds.

Because the methyl singlets in the **34b/35b** mixture occurred very close to other signals in the NMR spectrum, the ratio of **34b:35b** was assigned by comparison of the integrals of the lower field vinyl proton to that of the higher field vinyl proton. Because of similar overlap in the spectrum of the mixture of hydrindenes **34c** and **35c**, the ratio of **34c:35c** was also determined by comparison of the integrals of the vinyl signals.

Conclusions. Inspection of the data in Table I suggests three effects which influence the ratio of products from intramolecular cycloaddition: (1) The presence of the Y substituent (Y ≠ H) favors closure to a *trans*-hydrindene (compare **6a** with **6b**, **6c**, and **6d**). This is consistent with our original premise (that transition-state conformation C would be disfavored relative to conformation D); this effect has been noted recently by others. (2) The presence f the C-7 alkyl side chain favors closure to a *trans*-hydrindene. (Compare **6a** and **1a** or **1b**; **6b** and **5a**; **6c** and **5b**; **6d** and **5c**). This effect is apparent in hydrocarbon solvent but is not observed in DMA. (3) The use of dimethylaniline as the solvent for cycloaddition favors closure to a *trans*-hydrindene.[16] A solvent effect on the ratio of products from an intramolecular Diels–Alder reaction has been noted by Sternbach and by Williams.[17] In Sternbach's case[17a] the two products in question differed in the stereochemistry adopted by a substituent hydroxyl group. In the case described by Williams[17b] the products were regioisomers derived from a substrate containing two conjugated diene units. Our cycloadditions appear to be the first examples in which the ratio of cis- and trans-fused products varied with solvent.

The two substituent effects and the solvent effect do not appear to be additive in any simple way.

We have attempted to model the transition states for closure of nonatrienes by MM2; because MM2 values pertain to gas-phase energies, we might expect reasonable agreement with experiments run in nonviscous hydrocarbon solvents but not necessarily with experiments run in polar or viscous solvents such as DMA. The results of these calculations show the steric effects noted above (effects 1 and 2) as trends but have not, as yet, given values of $\Delta\Delta G^{\ddagger}$, i.e., $\Delta(G^{\ddagger}_{trans} - G^{\ddagger}_{cis})$, which correlate well with experiment. Refinement of our model for these transition states is the focus of ongoing effort.

The role of the solvent in ordering the relative stabilities of the transition states is not understood. It is conceivable that the change in product ratios is a manifestation of the porosity/viscosity effect on pericyclic reactions.[18]

Experimental Section

Dry pyridine, benzene, toluene, methylene chloride, cyclohexane, hexane, pentane, *N,N*-dimethylaniline, and DMF were obtained by distillation from CaH_2; dry THF and dry ether were obtained by distillation from sodium benzophenone ketyl. E. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. TLC's were performed on precoated EM silica gel 60 F-254 plates. Infrared spectra were recorded on a Perkin-Elmer 681 grating infrared spectrometer. Nuclear magnetic resonance spectra were recorded on Varian EM-360A spectrometer and are reported in δ units relative to tetramethylsilane as an internal standard. High field ^{1}H NMR were recorded on a Bruker WM-250 spectrometer. High-resolution mass spectra were obtained on a Kratos MS80 spectrometer at Brown University and at the Mass Spectroscopy Laboratory at the University of Pennsylvania. Microanalysis were performed by Schwarzkopf Microanalytical Laboratory.

Spectroscopic data for cyclization products given in this section represent mixtures obtained from the *N,N*-dimethylaniline experiments (procedure B).

General Procedure for Intramolecular Diels–Alder Reactions. A. In Benzene or Toluene in a Sealed Tube. A solution of 4–14 mg of the trienes in 5–20 mL of the solvent together with a small amount of 2,5-di-*tert*-butylhydroquinone (DTBH) or methylene blue was charged in a resealable pressure tube. The contents of the tube were cooled in liquid nitrog n. The tube was evacuated and sealed under vacuum. The cyclization was carried out under the conditions indicated in Table I. The tube was allowed to cool and was then opened and the solution was concentrated. The crude product was subjected to flash chromatography over silica gel with cyclohexane as eluent.

B. In *N,N*-Dimethylaniline. A solution of 5–10 mg of the triene and a small amount of 2,5-di-*tert*-butylhydroquinone in 1 mL of dry *N,N*-dimethylaniline (DMA) was stirred at reflux under nitrogen for the time indicated in Table I. The cooled solution was then diluted with 10 mL of ether and stirred with ~15 mL of 10% HCl for 30 min. The organic phase was washed several times with water. The dried solution was concentrated on a rotary evaporator. The resulting oily product was redissolved in ~0.5 mL of cyclohexane and filtered through dry silica gel.

Ethyl (*E*)- and (*Z*)-2-Bromo-2-nonenoate (8a). Procedure A. Heptaldehyde (114 mg, 1 mmol) was converted t α-bromo ester **8a** by the procedure of Boeckman.[7b] Flash chromatography (silica gel, 1:1 benzene/cyclohexane) gave the *E* isomer, R_f 0.48 (50 mg, 19%): ^{1}H NMR (60 MHz, $CDCl_3$) 0.80–1.75 (m, 11 H) 1.33 (t, J = 7 Hz, 3 H), 2.5 (q, J = 7 Hz, 2 H) 4.23 (q, J = 7 Hz, 2 H), 6.60 (t, J = 8 Hz, 1 H); IR (film) 2920, 2850, 1713, 1610, 1220. This was followed by the desired *Z* isomer, R_f 0.41 (206 mg, 78%): ^{1}H NMR (60 MHz, $CDCl_3$) 0.80–1.75 (m, 11 H), 1.33 (t, J = 7 Hz, 3 H), 2.34 (q, J = 7 Hz, 2 H) 4.25 (q, J = 7 Hz, 2 H), 7.23 (t, J = 8 Hz, 1 H); IR (film) 2920, 2845, 1728, 1625, 1255; HRMS, calcd for $C_{11}H_{19}BrO_2$ 264.0548 and 262.0568 for ^{81}Br and ^{79}Br, respectively, found 264.0556 and 262.0565.

(*Z*)-2-Bromo-2-nonen-1-ol (9a). Procedure B. Brom ester **8a** (840 mg, 3.2 mmol) was reduced with DIBAL.[7b] Distillati n (Kugelrohr, 150 °C, 0.4 mm) afforded 557 mg (79%) of a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 0.89–1.60 (m, 11 H), 2.15–2.24 (m, 2 H), 2.93 (br s, exchangeabl with D_2O, 1 H), 4.22 (br s, 2 H), 5.97 (t, J = 6 Hz, 1 H); IR (film) 3330 (br), 2920, 2845, 1650 (w), 1460; HRMS, calcd for $C_9H_{17}BrO$ 222.0442 and 220.0462, found 222.0437 and 220.0467.

(15) This designation is analogous to the well-known correlation for 14α- and 14β-$\Delta^{8,9}$ steroids; see: Bhacca, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field*; San Francisco: Holden Day, 1964; Tables 2-3 (pp 19–24).

(16) Parker, K. A.; Iqbal, T. *Tetrahedron Lett.* **1986**, *27*, 6291.

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(Z)-2-Bromo-2-nonenal (10a). Procedure C. To a stirred solution of 635 mg (2.87 mmol) of bromo alcohol **9a** in 15 mL of methylene chloride was added, at room temperature, 1.24 g (5.74 mmol) of PCC. The reaction mixture was stirred for 4 h. It was then diluted with 15 mL of ether and the organic solution was decanted. The residue was extracted three times with 5-mL portions of ether. The combined organic extract was concentrated to about 5 mL. The remaining chromium salts were removed by filtration through dry silica gel. Evaporation of the solvent and Kugelrohr distillation (140 °C, 1 mm) gave 541 mg (86% of a colorless liquid): ^{1}H NMR (60 MHz, $CDCl_3$) 0.80–1.80 (m, 11 H), 2.54 (q, J = 7.4 Hz, 2 H), 7.16 (t, J = 7.1 Hz, 1 H), 9.21 (s, 1 H); IR (film) 2920, 2850, 1700, 1615; HRMS, calcd for $C_9H_{15}BrO$ 220.0285 and 218.0305, found 220.0270 and 218.0287.

(Z)-3-Bromo-1,3-decadiene (11a). Procedure D. To a stirred suspension of 357 mg (1 mmol) of methyltriphenylphosphonium bromide in 5 mL of dry THF, under nitrogen, was added 0.60 mL (0.96 mmol, 1.6 M solution in hexane) of *n*-BuLi. The red solution was stirred for 5 min at room temperature and then the bromo aldehyde **10a** (73 mg, 0.33 mmol dissolved in 0.5 mL of THF) was added. The reaction mixture was stirred at room temperature for 4 h and then quenched with water. It was then partitioned between ether and water. The ether solution was washed twice with water, dried over anhydrous magnesium sulfate, and concentrated. The solvent was evaporated on a rotary evaporator. The residue was dissolved in 3 mL of pentane and excess phosphonium salt was filtered off. Evaporation of the solvent and Kugelr hr distillation afforded 61 mg (84%) of a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 0.86–0.91 (m, 3 H), 1.26–1.47 (m, 8 H), 2.31 (q, J = 7.2 Hz, 2 H), 5.15 (d, J = 10.6 Hz, 1 H), 5.52 (d, J = 16.3 Hz, 1 H), 5.98 (t, J = 7.2, 1 H), 6.31 (dd, J = 16.5, 10.8 Hz, 1 H); IR (film) 2920, 2840, 1630, 1600; HRMS, calcd for $C_{10}H_{17}Br$ 218.04193 and 216.0513, found 218.0463 and 216.0492.

(Z)-2-[(Phenylthio)methyl]-2-nonen-1-ol (9b). Procedure E. A solution of 100 mg (0.33 mmol) of ester **8b** in 2 mL of toluene was cooled to −78 °C under argon. To this stirred solution was added 0.6 mL of DIBAL (0.65 mmol, 1 M solution in hexane) dropwise. The reaction mixture was stirred for 30 min at −78 °C and then quenched with methanol and allowed to warm to room temperature. A few drops of water were added. The precipitate was filtered off and the filtate was washed with water and then dried over $MgSO_4$. Concentration and distillation (Kugelrohr) at 170 °C (1 mm) gave 81 mg (94%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 0.87 (t, J = 6.7 Hz, 3 H), 1.22 (m, 8 H), 1.67 (br s, exchangeable with D_2O, 1 H), 1.86–1.91 (m, 2 H), 3.66 (s, 2 H), 4.18 (s, 2 H), 5.56 (t, J = 7.3 Hz, 1 H), 7.17–7.53 (m, 5 H); IR (film) 3340 (br), 3050, 2920, 1580, 1475, 1435; HRMS, calcd f r $C_{16}H_{24}OS$ 264.1542, found 264.1545.

(Z)-2-[(Phenylthio)methyl]-2-nonenal (10b). Procedure F. To a cooled (0 °C) and stirred solution of 114 mg (0.303 mmol) of PDC in 1 mL of dry DMF was added, under nitrogen, a solution of 40 mg (0.152 mmol) of alcohol **9b** in 0.5 mL of DMF. The reaction mixture was stirred for 2 h and then partitioned between ether and water. The ether layer was washed with water, dried over $MgSO_4$, and concentrated. The crude product was filtered through a column of dry silica gel with benzene as eluent. Evaporation of solvent gave 29 mg (73% yield) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 0.89 (br s, 3 H), 1.21–1.40 (m, 8 H), 2.18 (q, J = 7 Hz, 2 H), 3.73 (s, 2 H), 6.56 (t, J = 7 Hz, 1 H), 7.22–7.51 (m, 5H), 9.37 (s, 1 H); IR (film) 3050, 2920, 2845, 2700, 1685, 1635; HRMS, calcd for $C_{16}H_{22}OS$ 262.1386, found 262.1383.

(Z)-3-[(Phenylthio)methyl]-1,3-decadiene (11b). Procedure G. To a solution of sodium methylsulfinyl methide prepared from sodium hydride (58 mg, 2.4 mmol) and dry Me_2SO (6 mL) was added under argon 967 mg (2.4 mmol) of methyltriphenylphosphonium iodide. The mixture was stirred for 30 min and then a solution of 210 mg (0.80 mm l) of aldehyde **10b** in 1 mL of Me_2SO was added. The reaction mixture was stirred for 6 h, then quenched carefully with water, and partitioned between ether and water. The ether layer was washed th roughly with water three times, dried, and concentrated. The residue was extracted with hexane and the hexane-soluble material was submitted to flash chromatography on silica gel with cyclohexane as eluent. This afforded 184 mg (88%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 0.87 (t, J = 6.5 Hz, 3 H), 1.24–1.31 (m, 8 H), 2.00 (q, J = 7.0 Hz, 2 H), 3.74 (s, 2 H), 5.04 (d, J = 10.8 Hz, 1 H), 5.24 (d, J = 17.5 Hz, 1 H), 5.62 (t, J = 7.4 Hz, 1 H), 6.29 (dd, J = 17.5, 10.8 Hz, 1 H), 7.19–7.41 (m, 5 H); IR (film) 3080, 3045, 2915, 2940, 1635, 1600. Anal. Calcd for $C_{17}H_{24}S$: C, 78.38; H, 9.31; S, 12.31. Found: C, 78.46; H, 9.40; S, 12.48.

Ethyl 7-Methyl-2(*E*),7-octadienoate (12a). Sodium hydride (595 mg, 12.4 mmol, 50% slurry in mineral oil) was washed with hexane under Ar. Anhydrous dimethoxyethane (30 mL) was added and the suspension was cooled to 0 °C. T this was added dropwise 2.77 g (12.4 mmol) of triethyl phosphonoacetate. The mixture was stirred for 20 min and then 925 mg (8.26 mmol) f aldehyde **7b** was added. The reaction mixture was stirred at 0 °C for 4 h and at room temperature for 2 h. It was then carefully quenched with water and partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether solution was washed twice with water, dried, and concentrated. The crude product was then submitted to flash chromatography on silica gel with 5:1 benzene/ether as eluent. This afforded 1.08 g (72% yield) of a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.30 (t, J = 7.5 Hz, 3 H), 1.73 (s, 3 H), 1.60–2.40 (m, 6 H), 4.17 (q, J = 7.5 Hz, 2 H), 4.70 (br s, 2 H), 5.79 (d, J = 15.5 Hz, 1 H), 6.98 (dt, J = 15.5 and 6.5 Hz, 1 H); IR (film) 3065, 2930, 1720, 1650, 1445, 1365; HRMS, calcd for $C_{11}H_{18}O_2$ 182.1306, found 182.1302.

7-Methyl-2(*E*),7-octadien-1-ol (13a). Compound **12a** was reduced to alcohol **13a** by procedure B. The crude product was distilled (Kugelrohr, 110 °C, 1.1 mm) to afford 401 mg (84% yield) of a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 1.41 (br s, exchangeable with D_2O, 1 H), 1.46–1.58 (m, 2 H), 1.71 (s, 3 H), 2.00–2.09 (m, 4 H), 4.08 (d, J = 4.4 Hz, 2 H), 4.67 (br s, 1 H), 4.71 (br s, 1 H), 5.58–5.76 (m, 2 H); IR (film) 3330 (br), 3065, 2925, 1647, 1445, 1370.

7-Methyl-2(*E*),7-octadienal (14a). Oxidation of 50 mg (0.36 mmol) of allylic alcohol **13a** by procedure F afforded 40 mg (81%) of **14a** as a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.72 (s, 3 H), 1.64–2.53 (m, 6 H), 4.74 (br s, 2 H), 6.10 (dd, J = 15.6, 7.80 Hz, 1 H), 6.87 (dt, J = 15.6, 6.2 Hz, 1 H), 9.51 (d, J = 7.8 Hz, 1 H); IR (film) 3065, 2930, 2730, 1690; HRMS, calcd for $C_9H_{14}O$ 138.1045, found 138.1028.

8-Methyl-1,3(*E*),8-nonatriene (6a). A sample of 421 mg (3.05 mmol) of aldehyde **14a** was transformed to triene **6a** by procedure D. Flash chromatography over silica gel with pentane as eluent afforded 245 mg, (59% yield) of a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 1.47–1.60 (m, 2 H), 1.71 (s, 3 H), 1.99–2.13 (m, 4 H), 4.67 (s, 1 H), 4.70 (s, 1 H), 4.96 (d, J = 9.9 Hz, 1 H), 5.09 (d, J = 16.8 Hz, 1 H), 5.71 (dt, J = 14.8, 7.4 Hz, 1 H), 6.06 (dd, J = 15.1, 10.4 Hz, 1 H), 6.31 (dt, J = 16.7, 10.1 Hz, 1 H); IR ($CHCl_3$) 3070, 2925, 1640, 1598, HRMS, calcd for $C_{10}H_{16}$, 136.1252, found, 136.1264.

Ethyl 2(*E*),7-Dimethyl-2,7-octadienoate (12a). A sample of 982 mg (8.77 mmol) of aldehyde **7b** was subjected to Emmons–Wadsworth reaction conditions as described in our previous paper[1] to afford a 9:1 mixture of *E* and *Z* isomers. These were separated by flash chromatography (silica gel, benzene). The *Z* isomer eluted first (R_f 0.43, 138 mg, 8% yield): ^{1}H NMR (60 MHz, $CDCl_3$) 1.34 (t, J = 7.5 Hz, 3 H), 1.73 (s, 3 H), 1.93 (s, 3 H), 1.53–2.66 (m, 6 H), 4.20 (q, J = 7.5 Hz, 2 H), 4.68 (br s, 2 H), 5.92 (t, J = 7.0 Hz, 1 H); IR (film) 3070, 2930, 1715, 1648. Further elution of the column with the same solvent afforded 1.22 g (71% yield) of the desired *E* ester as a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.32 (t, J = 7.5 Hz, 3 H), 1.75 (s, 3 H), 1.87 (s, 3 H), 1.56–2.36 (m, 6 H), 4.23 (q, J = 7.5 Hz, 2 H), 4.65 (br s, 2 H), 6.73 (t, J = 7.0 Hz, 1 H); IR (film) 3070, 2930, 1710, 1648, 1445, 1365. HRMS, calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1457.

2,7-Dimethyl-2(*E*)-octadien-1-ol (13b). A 100-mg sample (0.51 mmol) of ester **12b** was reduced to alcohol **13b** by procedure B to afford 70 mg (89%) of colorless product that was pure enough f r the next reacti n: ^{1}H NMR (60 MHz, $CDCl_3$) 1.68 (s, 3 H), 1.73 (s, 3 H), 1.50–2.25 (m, 6 H), 2.77 (br s, exchangeabl with D_2O, 1 H), 3.97 (s, 2 H), 4.68 (s, 2 H), 5.43 (t, J = 7.0 Hz, 1 H); IR (film) 3320 (br), 3065, 2920, 1648, 1450.

2,7-Dimethyl-2(*E*),7-octadienal (14b). Oxidation of 70 mg (0.45 mmol) f alcohol **13b** by procedure F afforded, after distillation (Kugelrohr, 90 °C, 1 mm), 61 mg (88%) of aldehyde **14b**: ^{1}H NMR (60 MHz, $CDCl_3$) 1.78 (two overlapping singlets, 6 H), 1.55–2.56 (m, 6 H), 4.72 (br s, 2 H), 6.52 (t, J = 7.0 Hz, 1 H), 9.42 (s, 1 H); IR (film) 3070, 2930, 2705, 1685, 1640; HRMS, calcd for

$C_{10}H_{16}O$ 152.1201, found 152.1200.

3,8-Dimethyl-1,3(*E*),8-n natriene (6b). Procedure D was applied to convert 71 mg (0.47 mmol) of aldehyde 14b to triene 6b (43 mg, 62% yield): ^{1}H NMR (250 MHz, $CDCl_3$) 1.53 (m, 2 H), 1.71 (s, 3 H), 1.73 (s, 3 H), 2.00–2.18 (m, 4 H), 4.67 (s, 1 H), 4.71 (s, 1 H), 4.93 (d, J = 10.4 Hz, 1 H), 5.08 (d, J = 17.3 Hz, 1 H), 5.49 (t, J = 7.3 Hz, 1 H), 6.37 (dd, J = 17.3 and 10.4 Hz, 1 H); IR (film) 3070, 2920, 1640, 1603; HRMS, calcd for $C_{11}H_{18}$ 150.1408, found 150.1404.

Ethyl (*Z*)-2-Bromo-7-methyl-2,7-octadienoate (12c). A sample of 800 mg (7.14 mmol) of aldehyde 7b was converted to br mo ester 12c by procedure A. The crude product was submitted to flash chromatography on silica gel using 1:1 benzene/cyclohexane as eluent. The *E* isomer eluted first (R_f 0.42, 190 mg, 10%): ^{1}H NMR (60 MHz, $CDCl_3$) 1.34 (t, J = 7.0 Hz, 3 H), 1.50–2.70 (m, 6 H), 1.74 (s, 3 H), 4.27 (q, J = 7.0 Hz, 2 H), 4.70 (br s, 2 H), 6.65 (t, J = 8.0 Hz, 1 H); IR (film) 3060, 2925, 1720, 1640, 1440, 1360. Further elution of the column with the same solvent system afforded 1.10 g (59% yield, R_f 0.38) of the *Z* isomer as a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.33 (t, J = 7.0 Hz, 3 H), 1.61–2.51 (m, 6 H), 1.76 (s, 3 H), 4.27 (q, J = 7.0 Hz, 2 H), 4.72 (br s, 2 H), 7.30 (t, J = 7.0 Hz, 1 H); IR (film) 3070, 2930, 1730, 1650, 1625, 1450; HRMS, calcd for $C_{11}H_{17}BrO_2$ 260.0411 and 262.0391, found 260.0400 and 262.0391.

(*Z*)-2-Bromo-7-methyl-2,7-octadien-1-ol (13c). A sample of 50 mg (0.19 mmol) of bromo ester 12c was reduced by procedure B to afford 40 mg (95%) of allylic alcohol 13c. The product was pure enough for the next step of the sequence: ^{1}H NMR (60 MHz, $CDCl_3$) 1.75 (s, 3 H) 1.10–2.30 (m, 6 H), 2.80 (br s, 1 H), 4.23 (br s, 2 H), 4.70 (br s, 2 H), 6.02 (t, J = 7.0 Hz, 1 H); IR (film) 3340 (br), 3070, 2930, 1650, 1450, 1375; HRMS, calcd for $C_9H_{15}BrO$ 218.0306 and 220.0286, found 218.0313 and 220.0312.

(*Z*)-2-Bromo-7-methyl-2,7-octadienal (14c). A sample of 40 mg (0.18 mmol) of bromo alcohol 13c was oxidized according to procedure C to afford 25 mg (63%) of the product: ^{1}H NMR (60 MHz, $CDCl_3$) 1.77 (s, 3 H), 1.55–2.73 (m, 6 H), 4.73 (br s, 2 H), 7.17 (t, J = 7.0 Hz, 1 H), 9.23 (s, 1 H); IR (film) 3060, 2920, 1700, 1645, 1615; HRMS, calcd for $C_9H_{13}BrO$ 216.0149 (for ^{79}Br), found 216.0151.

(*Z*)-3-Bromo-8-methyl-1,3,8-nonatriene (6c). A sample of 66 mg (0.30 mmol) of bromo aldehyde 14c was converted to bromo triene 6c by procedure D. The product was purified by flash chr matography on silica gel with cyclohexane as eluent (41 mg, 63%): ^{1}H NMR (250 MHz, $CDCl_3$) 1.53–1.65 (m, 2 H), 1.72 (s, 3 H), 2.06 (t, J = 7.9 Hz, 2 H), 2.32 (q, J = 7.2 Hz, 2 H), 4.69 (br s, 1 H), 4.72 (br s, 1 H), 5.16 (d, J = 10.3 Hz, 1 H), 5.53 (d, J = 16.4 Hz, 1 H), 5.99 (t, J = 7.2 Hz, 1 H), 6.32 (dd, J = 16.4 and 10.3 Hz, 1 H); IR (film) 3065, 2925, 1645, 1370.

Ethyl (*Z*)-2-[(Phenylthio)methyl]-7-methyl-2,7-octadienoate (12d). Procedure H. Sodium hydride (378 mg, 7.88 mmol, 50% suspension in mineral oil) was washed with dry hexane under an Ar atmosphere. Dry THF (60 mL) was added and the mixture was cooled to 0 °C. Thiophenol (867 mg, 7.88 mmol) was added to this stirred suspension. After 5 min, 1.86 g (7.88 mmol) of ethyl phosphonoacrylate was added dropwise and the mixture was stirred at 0 °C for 10 min. Then 882 mg (7.88 mmol) of aldehyde 7b was added dropwise and the mixture was stirred for 2.5 h. It was then partitioned between ether and water. The ether layer was washed twice with water and dried. Concentration followed by flash chromatography on silica gel with a 1:1 mixture of cyclohexane and benzene as eluent afforded 238 mg (10% yield, R_f 0.28) of the *E* isomer and 883 mg (37% yield, R_f 0.24) of the desired *Z* isomer as a colorless oil. Spectroscopic data for *Z* isomer: ^{1}H NMR (60 MHz, $CDCl_3$) 1.29 (t, J = 7.1 Hz, 3 H), 1.68 (s, 3 H), 3.80 (s, 2 H), 4.21 (q, J = 7.1 Hz, 2 H), 4.68 (br s, 2 H), 6.82 (t, J = 7.6 Hz, 1 H), 7.22–7.45 (m, 5 H); IR (film) 3065, 2930, 1710, 1645, 1582, 1478; HRMS, calcd for $C_{18}H_{24}O_2S$ 304.1497, found 304.1498.

(*Z*)-2-[(Phenylthi)methyl]-7-methyl-2,7-octadien-1-ol (13d). A sample of 200 mg (0.66 mmol) of ester 12d was reduced to allylic alcohol 13d by procedure B. This afforded after flash chromatogrpahy (silica gel, 16:1 benzene/ether) 138 mg (80% yield) of a colorless oil: ^{1}H NMR (60 MHz, $CDCl_3$) 1.70 (s, 3 H), 1.20–2.05 (m, 6 H), 2.37 (br s, exchanged with D_2O, 1 H), 3.63 (s, 2 H), 4.15 (br s, 2 H), 4.65 (br s, 2 H), 5.53 (t, J = 7.0 Hz, 1 H), 7.1–7.4 (m, 5 H); IR (film) 3350 (br), 3060, 2930, 1645, 1580, 1477, 1435; HRMS, calcd for $C_{18}H_{22}OS$ 262.1392, found 262.1390.

(*Z*)-2-[(Phenylthio)methyl]-7-methyl-2,7-octadienal (14d). Oxidation of 133 mg (0.51 mmol) of alcohol 13d by procedure F afforded, after distillation (Kugelrohr, 150 °C, 0.5 mm), 115 mg (87% yield) of a colorless oil: ^{1}H NMR (60 MHz, $CDCl_3$) 1.69 (s, 3 H), 1.28–2.38 (m, 6 H), 3.73 (s, 2 H) 4.67 (br s, 2 H), 6.56 (t, J = 7.0 Hz, 3 H), 7.12–7.57 (m, 5 H), 9.38 (s, 1 H); IR (film) 3085, 2930, 2705, 1685, 1635, 1580; HRMS, calcd for $C_{18}H_{20}OS$ 260.1235, found 260.1234.

(*Z*)-3-[(Phenylthio)methyl]-8-methyl-1,3,8-nonatriene (6d). Compound 14d (56 mg, 0.22 mmol) was converted to triene 6d by procedure G. Flash chromatography (silica gel, cyclohexane, R_f 0.23) afforded 37 mg (67% of yield) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 1.38–1.51 (m, 2 H), 1.68 (s, 3 H), 1.93–2.05 (m, 4 H), 3.74 (s, 2 H), 4.63 (br s, 1 H), 4.69 (br s, 1 H), 5.06 (d, J = 10.9 Hz, 1 H), 5.25 (d, J = 17.5 Hz, 1 H), 5.63 (t, J = 7.5 Hz, 1 H), 6.30 (dd, J = 17.5 and 10.9 Hz, 1 H), 7.17–7.41 (m, 5 H); IR (film) 3065, 2920, 1645, 1600, 1580; HRMS, calcd for $C_{17}H_{22}S$ 258.1442, found 258.1438.

Ethyl 2-Methyl-6-(phenylmethoxy)-2(*E*)-hexenoate (20). A sample of 2.4 g (50 mmol, 50% slurry in mineral oil) of NaH was washed with pentane under Ar. Anhydrous dimethoxyethane (200 mL) was added and the mixture was cooled to 0 °C. To this stirred suspension was added, dropwise, 11.9 g (50 mmol) of triethyl 2-phosphonopropionate. The mixture was stirred for 30 min and then 8.20 g (46.1 mmol) of benzyloxy aldehyde 19 was added dropwise. The reaction mixture was allowed to stir for 1 h and then quenched carefully with water. It was then partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether extract was washed with water, dried, and concentrated. The crude product was subjected to flash chromatography on silica gel with 4:1 benzene/ether to aff rd 11.0 g (89% yield) of a clear liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.27 (t, J = 7.0 Hz, 3 H), 1.87 (s, 3 H), 3.47 (t, J = 6.0 Hz, 2 H), 4.18 (q, J = 7.0 Hz, 2 H), 4.47 (s, 2 H), 6.80 (t, J = 7.5 Hz, 1 H), 7.17 (br s, 5 H); IR (film) 3080, 2930, 1705, 1647, 1450. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.47. Found: C, 73.23; H, 8.44.

2-Methyl-6-(phenylmethoxy)-2(*E*)-hexen-1-ol (21). A suspension of 1.61 g (42.4 mmol) of $LiAlH_4$ in 200 mL of dry ether was cooled to 0 °C. To this stirred mixture was added, dropwise, 10.5 g (40 mmol) of ester 20. The reaction mixture was allowed to stir at 0 °C for 30 min and then quenched carefully with water. After 30 min the reaction mixture was filtered. The filtrate was washed twice with water, dried over magnesium sulfate, and concentrated. Distillation (165 °C/1 mm) afforded 7.19 g (80% yield) of a colorless liquid: ^{1}H NMR (250 MHz, $CDCl_3$) 1.66 (s, 3 H), 1.68 (m, 2 H), 2.14 (q, J = 7.4 Hz, 2 H), 2.53 (br s, exchanged D_2O, 1 H), 3.47 (t, J = 6.4 Hz, 2 H), 3.99 (s, 2 H), 4.50 (s, 2 H), 5.40 (br t, J = 7.2 Hz, 1 H), 7.26–7.36 (m, 5 H); IR (film) 3380 (br), 3020, 2920, 1490, 1450. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 76.24; H, 9.41.

Propionate 22. A solution of 7.19 g (32.7 mmol) of alcohol 21 and 2.6 mL (33 mmol) of dry pyridine in 150 mL of dry CH_2Cl_2 was cooled to 0 °C. To this stirring solution was added dropwise 2.84 mL (32.7 mmol) of propionyl chloride. After the addition was over, the cooling bath was removed and the reaction mixture was allowed to stir for 30 min., It was then partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether solution was washed with water twice, dried, and concentrated. Distillation of the crude product (130 °C/1 mm) gave 7.53 g (83% yield) of a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) 1.15 (t, J = 8.0 Hz, 3 H), 1.68 (s, 3 H), 1.60–1.90 (m, 2 H), 2.00–2.55 (overlapping m, 4 H), 3.47 (t, J = 6.4 Hz, 2 H), 4.48 (s, 2 H), 5.47 (br t, J = 7.2 Hz, 1 H), 7.34 (br s, 5 H); IR (film) 3025, 2930, 2850, 1735, 1450. Anal. Calcd f r $C_{17}H_{24}O_3$: C, 73.86; H, 8.77. Found: C, 73.87; H, 8.79.

Erythro and Threo Acids 23. To a cooled (0 °C) and stirred solution of 677 mg (0.79 mL, 4.8 mmol) of cyclohexylisopropylamine in 6 mL of anhydrous THF, under Ar atmosphere, was added 2.4 mL (4.4 mmol, 1.55 M solution in hexane) of *n*-BuLi. After stirring for 10 min, the lithium cycl hexylisopropylamide thus prepared was cooled to −78 °C (dry ice/acetone). T this stirred solution was added 552 mg (2.00 mmol) of freshly distilled propionate 22 over a period of 10 min. After stirring for another 5 min, the cooling bath was removed; the reaction mixture was allowed to stir overnight and was then quenched with 10 mL of

0.1 N NaOH. The soluti n was extracted with ether twice (the ether washings were discarded). The aqueous layer was acidified with 10% HCl soluti n. The product was then extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried over $MgSO_4$ and concentrated to afford 423 mg (76%) of a viscous oil. The ^1H NMR (250 MHz, $CDCl_3$) showed it to be a mixture of erythro and threo isomers. The C_2 methyl appears as a doublet at 1.08 ppm (J = 5.0 Hz) for the erythro isomer and at 1.17 (J = 7.5 Hz) for the threo isomer. Other characteristic signals are at 1.57 (s, vinyl methyl, erythro isomer), 1.67 (s, vinyl methyl, threo isomer), 3.40–3.55 (m, 2 H), 4.47 (s, $C_6H_5CH_2$ erythro isomer), 4.49 (s, $C_6H_5CH_2$ threo isomer), 4.78 (s, 1 H), 4.87 (s, 1 H), 7.2–7.37 (m, 5 H), 9.95 (br, 1 H); IR (film) 3500–3000 (br), 1700, 1640, 1600, 1490, 1450; HRMS, calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1711.

Erythro and Threo Alcohols 24. To a cooled (0 °C) and stirred suspension of 490 mg (12.9 mmol) of LAH in 150 mL of dry ether was added dropwise a solution of 3.55 g (12.9 mmol) of carboxylic acid **24** in 5 mL of ether. The reaction mixture was stirred for 30 min and then quenched carefully with water. After 10 min, it was filtered and the filtrate was washed with water twice, dried ($MgSO_4$), and concentrated. The crude product was distilled (Kugelrohr, 140 °C, 0.9 mm) to afford 2.94 g (87%) of a colorless viscous liquid, shown by high field ^1H NMR (250 MHz, $CDCl_3$) to be 5:1 mixture of erythro and threo isomers. The C_2 methyl appears as a doublet at 0.89 ppm (J = 6.9 Hz) for the desired erythro isomer and at 0.97 ppm (J = 6.6 Hz) for the threo isomer. Other characteristic ^1H NMR signals are at 1.61 (s, 3 H), 3.43–3.70 (m, 4 H), 4.49 (s, 2 H), 4.69 (m, 1 H), 4.81 (m, 1 H), 7.33 (m, 5 H); IR (film) 3400 (br), 3060, 3020, 1640, 1490, 1450. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.80; H, 10.01. Found: C, 77.57; H, 10.21.

Tosylates 25. To a cooled (0 °C) and stirred solution of 500 mg (1.91 mmol) of a mixture of diastereoisomeric alcohols **24** in 10 mL of dry pyridine was added 546 mg (2.86 mmol) of *p*-toluenesulfonyl chloride. The cooling bath was then removed and the reaction mixture was allowed to stir for 6 h at room temperature. Excess *p*-toluenesulfonyl chloride was hydrolyzed by adding 10 mL of water and stirring for 15 min. The reaction mixture was partitioned between ether and water and the ether layer was washed twice with water, dried, and concentrated. The remaining pyridine residue was removed on a high vacuum line. The crude product was subjected to flash chromatography on silica gel with 40:1 benzene/ether as eluent to afford 578 mg (73%) of semisolid material: ^1H NMR (250 MHz, $CDCl_3$) 0.86 (d, J = 6.5 Hz, 2.5 H, C_2-methyl erythro isomer) 0.93 (d, J = 6.3 Hz, 0.5 H, C_2-methyl, threo isomer), 1.16–1.47 (m, 4 H), 1.53 (s, 3 H), 1.67–1.83 (m, 1 H), 1.88–1.97 (m, 1 H), 2.43 (s, 3 H), 3.35–3.40 (m, 2 H), 3.86–4.07 (m, 2 H), 4.47 (s, 2 H), 4.62 (br s, 1 H), 4.79 (br s, 1 H), 7.32 (m, 7 H), 7.78 (m, 2 H); IR (film) 3060, 3020, 1640, 1595, 1490, 1450; HRMS, calcd for $C_{24}H_{32}O_4S$ 416.2021, found 416.2001.

Benzyl Ethers 26. A solution of isopentylmagnesium bromide in a mixture of 10 mL of dry THF and 10 mL of dry ether was prepared by treating 600 mg (25 mmol) of magnesium with 3.67 g (24.3 mmol) of isopentyl bromide. To a solution of 578 mg (1.39 mmol) of tosylate **25** in 5 mL of dry ether and 5 mL of dry THF at −78 °C was added 0.70 mL (0.1 M solution in THF) of dilithium tetrachlorocuprate. To this rapidly stirring mixture was added the Grignard reagent dropwise. The solution was allowed to warm to room temperature and the stirring was continued for 6 h. It was then carefully quenched with 13% HCl solution. The product was partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether extract was washed twice with water. It was then dried, concentrated, and distilled (Kugelrohr, 120 °C, 0.3 mm) to afford 374 mg (85% yield) of a colorless oil: ^1H NMR (60 MHz, $CDCl_3$) 0.77–0.93 (m, 9 H), 0.23–1.80 (m, 13 H), 1.62 (s, 3 H), 3.43 (br t, J = 6.0 Hz, 2 H), 4.47 (s, 2 H), 4.63 (br s, 1 H), 4.80 (br s, 1 H), 7.30 (s, 5 H); IR (film) 3060, 3025, 1620, 1640, 1490, 1450. Anal. Calcd for $C_{22}H_{36}O$: C, 83.46; H, 11.49. Found: C, 83.16; H, 11.42.

Alc h l 27. To a stirred mixture of 367 mg (1.16 mmol) of benzyl ether **26**, 5 mL of dry ether, and 25 mL of liquid NH_3 were added small pieces of Na until th blue color persisted (approximately 200 mg). The solution was stirred for 5 min and then quenched with ethanol. The ammonia was allowed to evaporate at room temperature and the residue was partitioned between ether and water. The ether layer was washed with water, dried, and concentrated. Distillation (Kugelrohr, 140 °C, 0.3 mm) afforded 262 mg (quantitative yield) of a col rless viscous liquid. Anal. Calcd for $C_{15}H_{30}O$: C, 79.55; H, 13.38. Found: C, 79.64; H, 13.62. Separation of the two isomers was achieved by medium pressure chromatography (10:1 hexane/ethyl acetate at 10 psi, 31 × 2.5 cm column, silica gel). The erythro isomer (190 mg, 72%) was eluted first: ^1H NMR (250 MHz, $CDCl_3$) 0.80 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 1.00–1.56 (m, 13 H), 1.76 (m, 1 H), 3.62 (t, J = 6.4 Hz, 2 H), 4.65 (br s, 1 H), 4.79 (br s, 1 H); IR (film) 3320 (br), 3060, 2920, 1640, 1465, 1375. This was followed by 39 mg (15%) of the threo isomer: ^1H NMR (250 MHz, $CDCl_3$) 0.86 (d, J = 6.6 Hz, 6 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.95–1.56 (m, 13 H), 1.59 (s, 3 H), 1.76 (m, 1 H), 3.62 (t, J = 6.3 Hz, 2 H), 4.65 (br s, 1 H), 4.79 (br s, 1 H); IR (film) 3320, 3060, 1640, 1465, 1375.

Aldehyde 28. To a stirred suspension of 531 mg (5.31 mmol) of CrO_3 in 5 mL of dry CH_2Cl_2 was added 0.86 mL (10.6 mmol) of dry pyridine under an Ar atmosphere. The mixture was stirred for 15 min and then a solution of 200 mg (0.88 mmol) of alcoh l **27** in 1 mL of CH_2Cl_2 was added. The reaction mixture was stirred for 15 min and then diluted with 20 mL of ether. The soluti n was decanted and the tarry residue was extracted (4×) with 5-mL portions of ether. The combined ether extract was concentrated and then filtered through a column of dry silica gel. Evaporation of the solvent left a slightly yellowish liquid which was distilled (Kugelrohr, 90 °C, 0.25 mm) to afford 180 mg (91%) of a colorless oily liquid: ^1H NMR (250 MHz, $CDCl_3$) 0.80 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 6 H), 1.00–1.53 (m, 10 H), 1.56 (s, 3 H), 1.77 (m, 1 H), 2.35 (m, 2 H), 4.65 (s, 1 H), 4.81 (s, 1 H), 9.76 (s, 1 H); IR (film) 3060, 2710, 1725, 1640; HRMS, calcd for $C_{15}H_{28}O$ 224.2140, found 224.2157.

Ester 29a. A sample of 130 mg (0.58 mmol) of aldehyde **28** was transformed into (*E*)-2-methylacrylate **29** by the Emmons–Wadsworth procedure. The crude product was subjected to flash chromatography on silica gel (1:1 hexane/benzene). The *Z* ester (19 mg, 11% R_f 0.39) eluted first, followed by the desired *E* isomer (141 mg, 79%, R_f 0.31), an oily liquid: ^1H NMR (60 MHz, $CDCl_3$) signals for *E* isomer at 0.87 (d, J = 5.5 Hz, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.63 (s, 3 H), 1.83 (s, 3 H), 1.1–2.3 (m, 13 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.65 (br s, 1 H), 4.82 (br s, 1 H), 6.73 (t, J = 7.0 Hz, 1 H); IR (film) 3065, 2955, 1710, 1650; HRMS, calcd for $C_{20}H_{36}O_3$ 308.2715, found 308.2706.

Erythro Alcohol 30a. A sample of 161 mg (0.52 mmol) of ester **29a** was reduced by procedure B. Distillation (Kugelrohr, 150 °C, 1.4 mm) afforded 101 mg (73%) of a colorless oil: ^1H NMR (60 MHz, $CDCl_3$) 0.87 (d, J = 5.4 Hz, 6 H), 1.60 (two broad overlapping singlets, 6 H), 3.99 (s, 2 H), 4.66 (br s, 1 H), 4.79 (br s, 1 H), 5.39 (distorted t, J = 7.0 Hz, 1 H); IR (film) 3340 (br), 3070, 1645, 1415, 1380; HRMS, calcd for $C_{18}H_{34}O$ 266.2610, found 266.2620.

Erythro Aldehyde 31a. A sample of 101 mg (0.38 mmol) of alcohol **30a** was oxidized by procedure F to afford 69 mg (69%) of a colorless oil: ^1H NMR (60 MHz, $CDCl_3$) 0.88 (two overlapping doublets, J = 7 and J = 7 Hz, total integration 9 H), 1.67 (s, 3 H), 1.77 (s, 3 H), 4.69 (br s, 1 H), 4.84 (br s, 1 H), 6.47 (t, J = 7.0 Hz, 1 H), 9.39 (s, 1 H); IR (film) 3070, 2955, 2700, 1690, 1645; HRMS, calcd for $C_{18}H_{32}O$ 264.2453, found 264.2450.

Erythro Triene 5a. A 50-mg sample (0.19 mmol) of aldehyde **31a** was converted to triene **5a** by procedure D. Flash chromatography (silica gel, cyclohexane) of the crude product gave 31 mg (62%) of a colorless oil: ^1H NMR (250 MHz) 0.79 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 6 H), 1.60 (s, 3 H), 1.71 (s, 3 H), 0.99–2.13 (complex m, 13 H), 4.61 (s, 1 H), 4.79 (s, 1 H), 4.90 (d, J = 10.7 Hz, 1 H), 5.06 (d, J = 17.4 Hz, 1 H), 5.47 (t, J = 7.1 Hz, 1 H), 6.36 (dd, J = 10.7 and 17.4 Hz, 1 H); IR (film) 3065, 1640, 1605, 1465, 1380; HRMS, calcd for $C_{19}H_{34}$ 262.2661, found 262.2669.

Bromo Ester 29b. Procedure A was applied to 180 mg (0.8 mm l) of aldehyde **28**. The crude product was subjected to flash chromatography n silica gel (2:1 cyclohexane/benzene) to separate the two geometric isomers. The (*E*)-2-bromoacrylate (31 mg, 10%, R_f 0.28) eluted first: ^1H NMR (250 MHz, $CDCl_3$) 0.79 (d, J = 6.9 Hz, 3 H), 0.87 (two superimposed d, J = 6.6 Hz and J = 6.6 Hz, 6 H), 1.33 (t, J = 6.8 Hz, 3 H), 1.59 (s, 3 H), 2.23–2.52 (m, 2 H), 4.25 (q, J = 6.8 Hz, 2 H), 4.65 (br s, 1 H), 4.80 (br s, 1 H), 6.65 (t, J = 6.8 Hz, 1 H). Further elution with the sam solvent system afforded 140 mg (47%, R_f 0.24) of the desired

(*Z*)-2-br moacrylate: ^{1}H NMR (250 MHz, $CDCl_3$) 0.80 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.62 (s, 3 H), 2.06–2.38 (m, 2 H), 4.27 (q, J = 7.1 Hz, 2 H), 4.69 (br s, 1 H), 4.83 (br s, 1 H), 7.30 (t, J = 7.1 Hz, 1 H); IR (neat) 3060, 1720, 1640, 1620, 1460; HRMS, calcd f r $C_{19}H_{33}O_2{}^{81}Br$ 374.1643, found 374.1650.

Bromo Alcoh l 30b. Procedure B was applied to convert 80 mg (0.21 mmol) f bromoacrylate **29b** to allylic alcohol **30b** (61 mg, 85%) which was pure enough for the next step of the sequence: ^{1}H NMR (250 MHz) 0.79 (d, J = 6.9 Hz 3 H), 0.87 (two overlapping d, J = 6.6 Hz, and J = 6.6 Hz, 6 H), 1.00–2.20 (complex m, 14 H), 1.61 (s, 3 H), 4.24 (d, J = 7.4 Hz, 2 H), 4.67 (br s, 1 H), 4.82 (br s, 1 H), 6.01 (t, J = 7.1 Hz, 1 H); IR (film) 3330 (br), 3060, 2940, 1640, 1460, 1370; HRMS, calcd for $C_{17}H_{31}O^{81}Br$ 332.1538, found 332.1558.

Bromo Aldehyde 31b. A 200-mg sample (0.60 mmol) of bromo alcohol **30b** was transformed into bromo aldehyde **31b** by procedure F at room temperature. Evaporation of the solvent under reduced pressure left 125 mg (63% yield) of an oil: ^{1}H NMR (250 MHz) 0.82 (d, J = 6.9 Hz, 3 H), 0.87 (two superimposed d, J = 6.6 Hz and J = 6.6 Hz, 6 H), 1.63 (s, 3 H), 1.13–1.88 (complex m, 11 H), 2.26–2.56 (m, 2 H) 4.71 (br s, 1 H), 4.86 (br s, 1 H), 7.16 (t, J = 7.1 Hz, 1 H), 9.20 (s, 1 H); IR (film) 3060, 1695, 1635, 1610, 1460; HRMS, calcd for $C_{17}H_{29}{}^{81}BrO$ 330.1381, found 330.1391.

Bromo Triene 5b. A sample of 200 mg (0.61 mmol) of bromo aldehyde **31b** was converted into bromo triene **5b** by procedure D. Flash chromatography on silica gel (hexane) gave 118 mg (59%) f a colorless liquid: ^{1}H NMR (250 MHz) 0.80 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 6 H), 1.62 (s, 3 H), 1.10–1.83 (complex m, 11 H), 2.02–2.35 (m, 2 H), 4.68 (br s, 1 H), 4.82 (br s, 1 H), 5.15 (d, J = 10.2 Hz, 1 H), 5.51 (d, J = 16.0 Hz, 1 H), 5.99 (t, J = 7.1 Hz, 1 H), 6.30 (dd, J = 10.2 and 16.1 Hz, 1 H); IR (film) 2920, 1640, 1630, 1455, 1370; HRMS, calcd for $C_{19}H_{31}{}^{81}Br$ 328.1589, found 328.1571.

(*E*)-Thiophenyl Ester 29c. Application of procedure H to 342 mg (1.53 mmol) of aldehyde **28** provided ester **29c** and its *Z* isomer. This mixture was subjected to flash chromatography (2:1 cyclohexane/benzene). The *Z* isomer (19 mg, 3%) was f ll wed by 52 mg (9%) of mixed fractions. Further elution of th column afforded 345 mg (59%) of the desired *E* isomer **29c** as an ily liquid. Spectroscopic data for the *Z* isomer: ^{1}H NMR (250 MHz, $CDCl_3$) 0.76 (d, J =6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6 H), 0.96–1.70 (m, 11 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.55 (s, 3 H), 2.12–2.41 (m, 2 H), 3.70 (s, 2 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.57 (br s, 1 H), 4.75 (br s, 1 H), 5.79 (t, J = 7.6 Hz, 1 H) 7.20–7.38 (m, 5 H); IR (film) 3060, 2920, 1715, 1640. Spectroscopic data for the *E* isomer: ^{1}H NMR (60 MHz, $CDCl_3$) 0.78–0.86 (m, 9 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.56 (s, 3 H), 3.78 (s, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 4.62 (br s, 1 H), 4.77 (br s, 1 H), 6.82 (t, J = 7.4 Hz, 1 H), 7.17–7.51 (m, 5 H); IR (film) 3065, 2940, 1710, 1640; HRMS, calcd for $C_{28}H_{40}O_2S$ 416.2749, found 416.2743.

(*Z*)-Thiophenyl Alcohol 30c. A solution of 295 mg (0.709 mmol) of ester **29c** in 5 mL of dry toluene was cooled to −78 °C under Ar atmosphere. To this stirred solution was added 2.0 mL (2.83 mmol, 1.41 M solution in hexane) of diisobutylaluminum hydride. The reaction mixture was stirred for 15 min and then quenched with few drops of water. It was then allowed to warm to room temperature and stirred for 15 min. The precipitate was filtered off and the filtrate was washed with water, dried ($MgSO_4$), and c ncentrated to afford 263 mg (quantitative yield) of a colorless oil. This product was used in the next experiment without further purification: ^{1}H NMR (60 MHz, $CDCl_3$) signals at 0.88 (d, J = 5.5 Hz, 6 H), 1.58 (s, 3 H), 3.66 (s, 2 H), 4.20 (br s, 2 H), 4.63 (s, 1 H), 4.77 (s, 1 H), 5.57 (t, J = 7.0 Hz, 1 H), 7.15–7.45 (m, 5 H); IR (film) 3360 (br), 3060, 1640, 1580; high-resolution mass spectrum, calcd for $C_{24}H_{38}OS$ 374.2644, found 374.2638.

(*Z*)-Thiophenyl Aldehyd 31c. Oxidation of 263 mg (0.70 mmol) of alcohol **30c** according to procedure F afforded 217 mg (82% from ester **29c**) of aldehyde **31c**: ^{1}H NMR (60 MHz, $CDCl_3$) signals at 0.87 (d, J = 5.5 Hz, 6 H), 1.56 (s, 3 H), 3.72 (s, 2 H), 4.65 (s, 1 H), 4.82 (s, 1 H), 6.57 (t, J = 7.8 Hz, 1 H), 7.17–7.45 (m, 5 H), 9.38 (s, 1 H); IR (film) 3060, 2920, 2705, 1685, 1640; HRMS, calcd for $C_{24}H_{36}OS$ 372.2487, found 372.2486.

Thi phenyl Triene 5c. A sample of 217 mg (0.58 mmol) of aldehyde **31c** was converted to triene **5c** by procedure G. Flash chromatography on silica gel (cyclohexane) afforded 174 mg (81%) of a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) 0.77 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 0.97–2.45 (complex multiplets, 13 H), 1.56 (s, 3 H), 3.72 (AB quartet, J = 11.6 Hz, 2 H, $PhSCH_2$), 4.61 (s, 1 H), 4.76 (s, 1 H), 5.04 (d, J = 10.9 Hz, 1 H), 5.24 (d, J = 17.5 Hz, 1 H), 5.62 (t, J = 7.5 Hz, 1 H), 6.28 (dd, J = 17.5, 10.9 Hz, 1 H), 7.19–7.40 (m, 5 H); IR (film) 3060, 2945, 1640, 1600, 1530; HRMS, calcd f r $C_{25}H_{32}S$ 370.2695, f und 370.2685.

Hydrindenes 32a + 33a: ^{1}H NMR (250 MHz, $CDCl_3$) 0.71 (s, methyl of **32a**, 1.3H), 0.97 (s, methyl of **33a**, 1.7 H), 1.15–2.14 (unresolved multiplets, 11 H), 5.51–5.72 (m, 2H); IR ($CHCl_3$) 2920, 1460, 1375, 1110 cm^{-1}; HRMS, calcd for $C_{10}H_{16}$ 136.1252, found 136.1260.

Hydrindenes 32b + 33b: ^{1}H NMR (250 MHz) 0.70 (s, 2.35 H, angular methyl of **32b**) 0.95 (s, 0.65 H, angular methyl of **33b**), 1.6 (br s, 3H), 1.55–1.77 (complex m, 8 H), 1.90–2.15 (m, 3 H), 5.20 (br s, 0.78 H, vinyl H of **32b**), 5.30 (br s, 0.22 H, vinyl H of **33b**); IR ($CHCl_3$) 2920, 1450, 1370 cm^{-1}; HRMS, calcd for $C_{11}H_{18}$ 150.1408, found 150.1399.

Hydrindenes 33c + 33c: ^{1}H NMR (250 MHz) 0.81 (br s, 1.5 H, methyl of **32c**), 1.03 (s, 1.5 H, methyl of **33c**), 1.26–2.44 (complex m, 11 H), 5.88 (q, J = 4.0 Hz, 0.5 H), 5.97 (t, J = 4.0 Hz, 0.5 H); IR ($CHCl_3$) 2950, 1670, 1450, 1370 cm^{-1}.

Hydrindenes 32d + 33d: ^{1}H NMR (250 MHz) 0.70 (s, 1.9 H, angular methyl of **32d**) 0.90 (s, 1.1 H, angular methyl of **33d**), 1.13–2.21 (complex m, 11 H), 3.41–3.61 (m, 2H), 5.36 (br s, 0.63 H, vinyl H of **32d**), 5.48 (br s, 0.37 H, vinyl H of **33d**).

34a and 35a. The crude reaction mixture from the cyclization of triene **5a** was subjected to silver nitrate chromatography with hexane as eluent. The desired trans isomer **34a** was eluted first, ($AgNO_3$ TLC R_f 0.30, 18 mg, 69%): ^{1}H NMR (250 MHz, $CDCl_3$) 0.67 (s, 3 H), 0.87 (d, J = 6.6 Hz, 6 H), 0.94 (d, J = 6.5 Hz, 3 H), 1.61 (s, 3 H), 1.01–2.12 (complex m, 18 H), 5.21 (br s, 1 H); IR (neat) 2900, 1655 (w), 1460, 1370 cm^{-1}; HRMS, calcd for $C_{19}H_{34}$ 262.2660, found 262.2655. Further elution with the same solvent afforded the cis isomer **35a** ($AgNO_3$ TLC R_f 0.13, 6 mg, 23%): ^{1}H NMR (250 MHz, $CDCl_3$) 0.87 (d, J = 6.6 Hz, 6 H), 0.89 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 1.01–1.95 (complex m, 18 H), 5.36 (br s, 1 H); IR (neat) 2940, 1460, 1370 cm^{-1}; HRMS, calcd for $C_{19}H_{34}$ 262.2660, found 262.2649.

Hydrindenes 34b + 35b: ^{1}H NMR (250 MHz) 0.78 (s, 1.93 H), 0.87 (d, J = 6.9 Hz, 6 H), 0.91 (d, J = 6.3 Hz, 1.07 H), 0.92 (d, J = 6.6 Hz, 1.93 H), 0.95 (s, 1.07 H), 1.10–2.52 (unresolved m, 18 H), 5.89 (m, 0.64 H), 6.00 (m, 0.36 H); IR (neat) 2910, 1630, 1460, 1370 cm^{-1}; HRMS, calcd for $C_{18}H_{31}Br^{81}$ 328.1589, f und 328.1575.

Hydrindenes 34c + 35c: ^{1}H NMR (250 MHz) 0.67 (s, 2.14 H), 0.87 (d, overlapping with s at 0.89, 6.86 H), 0.93 (d, J = 6.65 Hz, 3 H), 1.10–2.15 (unresolved m, 18 H), 3.41–3.59 (m, 2H), 5.37 (br s, 0.72 H), 5.54 (br s, 0.28 H), 7.13–7.36 (m, 5H); IR (neat) 2900, 1580, 1470; HRMS, calcd for $C_{28}H_{38}S$ 370.2695, found 370.2671.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-8306687). The Bruker WM-250 NMR spectrometer used in this work was purchased with funds provided by the NSF and the Montedison Group of Milan; the Kratos MS80 spectrometer at Brown University was purchased with funds provided by the Division of Research Resources of the Department of Health and Human Services.

Registry No. **1a**, 109308-31-8; **1b**, 109308-32-9; **2a**, 109428-83-3; **2b**, 109308-33-0; **3a**, 109428-84-4; **3b**, 109363-29-3; **5a**, 109308-15-8; **5b**, 109333-72-4; **5c**, 109308-16-9; **6a**, 109307-86-0; **6b**, 109307-87-1; **6c**, 109307-88-2; **6d**, 109307-89-3; **7b**, 64825-78-1; (*E*)-**8a**, 109307-66-6; (*Z*)-**8a**, 109333-95-1; **8b**, 64600-37-9; **9a**, 109307-69-9; **9b**, 109432-19-1; **10a**, 109307-68-8; **10b**, 109307-70-2; **11a**, 109307-71-3; **11b**, 109307-72-4; **12a**, 109307-73-5; (*E*)-**12b**, 109307-74-6; (*Z*)-**12b**, 109307-75-7; (*E*)-**12c**, 109307-76-8; (*Z*)-**12c**, 109307-77-9; (*E*)-**12d**, 109307-79-1; (*Z*)-**12d**, 109307-80-4; **13a**, 77350-75-5; **13b**, 71547-65-4; **13c**, 109307-81-5; **13d**, 109307-82-6; **14a**, 109307-83-7; **14b**, 109307-84-8; **14c**, 109390-16-1; **14d**, 109307-85-9; **15**, 21856-89-3; **16**, 5212-80-6; **17**, 110-63-4; **18**, 4541-14-4; **19**, 5470-84-8; **20**, 109307-90-6; **21**, 109307-91-7; **22**, 109307-92-8; *erythro*-**23**, 109307-93-9; *threo*-**23**, 109307-94-0; *er-*

ythro-24, 109307-95-1; *threo*-24, 109307-96-2; *erythro*-26, 109307-99-5; *threo*-26, 109308-00-1; *erythro*-27, 109308-01-2; *threo*-27, 109308-02-3; (*Z*)-29a, 109308-03-4; (*E*)-29a, 109308-04-5; (*E*)-29b, 109308-05-6; (*Z*)-29b, 109308-06-7; (*Z*)-29c, 109308-07-8; (*E*)-29c, 109308-08-9; 30a, 109308-09-0; 30b, 109308-10-3; 30c, 109308-11-4; 31a, 109308-12-5; 31b, 109308-13-6; 31c, 109308-14-7; 32a, 109308-23-8; 32b, 109308-25-0; 32c, 109308-27-2; 32d, 109308-29-4; 33a, 109308-24-9; 33b, 109308-26-1; 33c, 109308-28-3; 33d, 109308-30-7; 34a, 109308-17-0; 34b, 109308-19-2; 34c, 109308-21-6; 35a, 109308-18-1; 35b, 109308-20-5; 35c, 109308-22-7; *erythro*-48, 109307-97-3; *threo*-48, 109307-98-4; (α-bromocarbethoxy)methylenetriphenylphosphorane, 109307-65-5; ethyl phosphonoacrylate, 109307-78-0; heptaldehyde, 111-71-7; methyltriphenylphosphonium bromide, 1779-49-3; methyltriphenylphosphonium iodide, 2065-66-9; triethyl 2-phosphonopropionate, 3699-66-9; vitamin D, 1406-16-2.

Notes

Methanesulfonanilides and the Mannich Reaction

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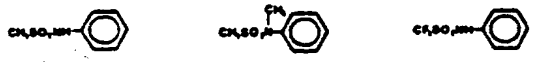
Received December 15, 1986

Numerous reviews on the Mannich reaction have appeared.[1] The reaction of phenols under typical Mannich conditions (i.e., amine and aqueous formaldehyde in alcoholic solvents) affords preponderantly ortho aminomethylation products,[2] which is consistent with a quasi six-membered transition-state mechanism.[3] The use of methanesulfonanilide (1) (pK_a = 9.9)[4] in the Mannich reaction has not previously been reported although the acidity is similar to that of phenol (pK_a = 11.0). We now report our investigations on the reaction of various methanesulfonanilides under typical Mannich conditions.

Methanesulfonanilides 1–10 (Table I) were prepared in good to excellent yields by using a modification of the procedure of Marvel et al.[5] (see Experimental Section). Reaction of methanesulfonanilide 1 with pyrrolidine (pK_a = 11.27)[6] and aqueous formaldehyde in hot ethanol (reaction mixture pH 8.0) affords only the para-substituted aminomethylation product 11 (Table II). This is evident from the 300-MHz NMR spectrum of 11, which displays the aromatic protons as an AB quartet centred at δ 7.40 with J_{AB} = 8.0 Hz and $\Delta\nu_{AB}$ = 26.8 Hz. Similar results were obtained by using diethylamine (pK_a = 10.49)[6] and piperidine (pK_a = 11.12)[6] as the secondary amines (Table II, 12 and 13). In each case the product can be obtained by filtering the concentrated reaction mixture through a sh rt column of alumina.[7] This reaction does not appear to be reversible since submitting pure 13 to the reaction conditions does not lead to production of 1 (TLC analysis) and 13 was isolated unchanged. Addition of a catalytic amount of HCl to the reaction mixture or limiting the amounts of formaldehyde used to 1.1 equiv did not improve the chemical yield, although these conditions are sometimes the method of choice for the Mannich reaction.[1] *N*-Methylmethanesulfonanilide (21)[8] does not react with the pyrrolidine/formaldehyde mixture, demonstrating that the NH group is essential for reactivity. Similarly, trifluoromethanesulfonanilide (22) (pK_a = 4.45)[9] was recovered unchanged from the reaction mixture, indicating that pK_a is also an important aspect of this transformation.



1 21 22

No aminomethylation products were observed when methanesulfonanilide (1) was treated with either ethylbenzylamine (pK_a = 9.64)[10] or benzylamine (pK_a = 9.33)[6] under the usual reaction conditions. This is attributed to the lower basicity of these amines.

Methanesulfonanilides 3 and 9 failed to react with the pyrrolidine/formaldehyde mixture. Deactivated systems do react, albeit in poor yield, with mostly starting material being recovered (Table II, 14, 17, and 19).

The position of the pyrrolidinylmethyl group in adducts 14 and 17 was determined by proton NOE difference NMR. Selective irradiation of the benzylic methylene protons (δ 3.57) of 14, which were well-resolved in the spectrum, resulted in enhancement of two aromatic protons (δ 7.24 and 7.44). This is consistent only with two aromatic ortho protons as in structure 14. Similarly, irradiation of the methoxy protons (δ 3.79) of 17 resulted in enhancement of two aromatic protons (δ 6.69 and 6.82). This allows for the assignment of the pyrrolidinylmethyl group to the 2-position of the aromatic ring as in 17.

Aminomethylation takes place only on the acetyl methyl group of compound 7. Similar results were reported by Gallo and Comer[11] for this substrate using acidic condi-

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